CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-251

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

DEC 11 1995

Clinical Pharmacology & Biopharmaceutics Review

INFASURF®
Intratracheal Suspension
(Calf Lung Surfactant Extract)

NDA 20-521

Ony, Incorporated
Amherst, NY

Type of Submission:
NDA, NME, 1S

Submission Date:
July 27, 1995

Reviewer:
Brad Gillespie, PharmD

BACKGROUND INFASURF is intended to be used intratracheally for the prevention and treatment of Respiratory Distress Syndrome (RDS) in premature neonates. Clinical data has been submitted for two parallel, active controlled trials comparing INFASURF to EXOSURF NEONATAL®. Safety of the product has been demonstrated in open clinical trials involving in excess of 14,000 patients.

PHARMACOKINETICS Conventional bioavailability/pharmacokinetic studies were not performed with INFASURF. The sponsor provides the following rationale for this omission:

1) The drug is administered and acts locally (luminal surface of the alveolar epithelium). Systemic absorption is minimal.

2) The target population is so medically fragile, that such studies would carry high risks of acute and long term morbidity. The sponsor specifically notes that:
   (a) Premature and newborn infants are not acceptable candidates for radiolabel studies
   (b) Drawing excessive blood in these patients with minimal blood volumes is an unacceptable risk
   (c) Installation of liquid into the lungs of an infant after the onset of breathing without a specific therapeutic intent carries a significant risk of severe vagal cardiopulmonary responses or interruption of ventilation

Thus, the sponsor requests a waiver of the requirement for evidence of *in vivo* bioavailability under 21 CFR 320.22 (e).

DISCUSSION Two neonatal pulmonary surfactants have received FDA approval for marketing:
(a) EXOSURF® (Colfosceril, Burroughs Wellcome Company), a totally synthetic, protein-free product approved in August, 1990.
(b) SURVANTA® (Beractant, Ross Laboratories), a bovine extract approved in July, 1991.

Neither sponsor was required to perform human bioavailability/pharmacokinetic studies (see

Dr Pradheep Sathe's Biopharmaceutics review of the colfosceril bio-waiver request of October, 1990).

CFR 320.22 (e) states that FDA may for good cause waive a requirement for the submission of evidence of *in vivo* bioavailability if that waiver is compatible with the protection of the public health.

CONCLUSION The product described in this submission appears to fit the criteria used to waive human bioavailability requirements in earlier pulmonary surfactant submissions.

RECOMMENDATION The Office of Clinical Pharmacology & Biopharmaceutics has reviewed the sponsor's request to waive the requirement for submitting evidence of *in vivo* bioavailability (21 CFR 320.22 (e)) and agree that this waiver should be granted.

12/11/95

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

FT 12/11/95

Dale P. Conner, PharmD, Team Leader

cc:
HFD-570 (NDA20-521, Divisional File, Kuzmik, Pina)
HFD-870 (Conner, ChenM, Hunt, Gillespie)
HFD-880 (Fleischer)
HFD-860 (Malinowski)
HFD-850 (Lesko, Chron, Drug, Reviewer)
HFD-340 (Viswanthan)
HFD-205 (FOI)

DEC 8 1995

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Ony, Incorporated
Amherst, NY

Type of Submission:
NDA, NME, 1S
Submission Date:
March 13, 1995
Reviewer:
Brad Gillespie, PharmD

BACKGROUND INFASURF is intended to be used intratracheally for the prevention and treatment of Respiratory Distress Syndrome (RDS) in premature neonates. Clinical data have been submitted for two parallel, active controlled trials comparing INFASURF to EXOSURF NEONATAL®. Safety of the product has been demonstrated in open clinical trials involving in excess of 14,000 patients.

DISCUSSION This submission was considered fileable from a clinical perspective. However, it was determined that this product is not fileable since it infringes on the orphan drug exclusivity of the approved product SURVANTA® (Beractant, Ross Laboratories).

ACTION Since the Division of Pulmonary Drug Products refused to file this application, no action by the Office of Clinical Pharmacology & Biopharmaceutics is necessary at this time.

12/8/95
Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

FT 12/8/95
Dale P. Conner, PharmD, Team Leader

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